Method of Diagnosis and Treatment and Related Compositions and Apparatus

Related Applications

This application claims priority of the provisional application filed Jan. 31, 1996 as 60/010,881 of the United States Patent and Trademark Office.

Background of the Invention

I. Field of the Invention

This invention deals with medicine and the diagnosis and treatment of certain types of blood vessel diseases and a variety of disorders which all have been discovered to have in common a condition called "Vasospasm" or "Narrowing of the Blood Vessels."

II. Description of the Prior Art

The most relevant prior art appears to be:

1. Roger P. Woods, Marco Iacoboni, M.D., Ph.D., and John C. Mazziotta, M.D., Ph.D.; Brief Report: Bilateral Spreading Cerebral Hypoperfusion during Spontaneous Migraine Headache. N Engl J Med 1994; 331; 1689-92.

2. M. Hennerici, M.D., W. Rautenberg, M.D., G. Sitzer, M.D., and A. Schwartz, M.D.; Transcranial Doppler Ultrasound for the Assessment of Intracranial Arterial Flow Velocity - Part 1, Examination Technique and Normal Values; Surg Neurol 1987; 27; 439-48.

3. U.S. patents 5,309,923 to Leuchter and Cook, 5,307,807 to Sosa et al, 5,287,859 to Erwin describe "qEEG" devices and techniques useful with the invention.

4. U. S. patent 5,163,444 to Braverman discusses the P300 brain waves mentioned below.

III. Problems Presented by Prior Art

Prior treatment regimens have generally focused on the acute disease while the present invention embodies the discovery that the vasospasms and vascular narrowings are commonly chronic in nature. Further, past dosages have often been excessive and such over-dosages are found by applicant's investigations to actually be harmful in patients at some stages, because such dosages can themselves subtlety promote vasospasms.

Summary of the Invention

I. General Statement of the Invention

It is an object of this invention to treat vascular spasm as identified primarily from ultrasound, but which may be suspected on the clinical grounds, with the use of vasodilators in a progressive step-wise fashion, preferably titrated against continuing testing. The introduction usage of the medications and tapering of the medications must be done in a specific fashion in order to result in a clinical improvement of the patient in a variety of conditions which all have in common the presence of vascular spasm. Certain of these conditions have not previously been identified as having vascular spasm as a component of their disorder, and these conditions have been identified in applicant's clinical practice and thus will be named further under the section that deals with claims. It has been recognized that patients with vascular spasm have a typical clinical presentation of symptoms, and that these symptoms follow a progression in substantially direct correlation to the vascular spasm identified on Transcranial Doppler (TCD), a technique using ultrasound imaging of the brain for evaluation of vascular size. It is further recognized clinically that vascular dilation medications may have paradoxical responses depending upon dose. In essence, there is a therapeutic window, a dose which is the proper dose for treatment of the condition which changes over time. Initially under dosing the patient will result in no change of their symptoms, as well as overdosing the patient will result in the exact same symptoms as under dosing the patient or giving the patient no medication at all. Thus vascular dilation medications tend to have a paradoxical response with overdose. The proper dosage for a patient is based upon clinical response in association with objective data as may be identified from Transcranial Doppler ultrasound as well as other imaging modalities.

Essentially the preferred methodology is to obtain an image or measurement of the intracranial blood vessels in the diseased conditions to be noted under Claims, and then introduce low dose vasodilation medications. Repeat ultrasounds or other imaging modalities are used to titrate the patient's medical response. As vascular dilatation occurs, medications hen become altered in a stepwise tapering fashion, using ultrasound or other imaging modalities to identify the redevelopment of vasospasm and the appropriate dosage of medication. It is recognized that patients' metabolism may vary across the course of the time that they are on these medications, and it is further recognized that patients' clinical symptoms may not be a useful guide to their response to medication. Accordingly, repeat evaluations with the use of imaging modalities are used to assess pharmacological response.

The invention comprises a method of treating a patient presenting with symptoms suggestive of a stroke or multiple sclerosis (MS) and/or reporting trauma to the neck and/or head e.g. whiplash or concussion from a fall or any other disease discovered to be alleviatable by relaxation of smooth muscle or to comprise vasospasm, preferably intracranial vasospasm as a symptom; comprising in combination:

a) testing by determining rate of blood flow, preferably intercranially or in the arteries of the neck and or upper back, and/or determining relative diameter of those vessels e.g. by magnetic resonance imaging (MRI) and/or determining evoked potential;

b) treating the patient with an effective dosage of a vasodilator, preferably nitroglycerin administered by patch, preferably at a rate less than about 0.8 mg/hr;

c) re-determining said rate or diameter or potential (collectively "blood flow") after said treatment, to evaluate recurrence of vasospasm;

d) adjusting the dosage in response to the results of the re-determining;

whereby symptoms comprising headache, burning sensation or pain in the head dizziness, or fainting, etc., or other symptoms of the disease treated, are alleviated.

Disease: The technique and associated compositions are valuable in the treatment of any condition in which vasospasms, preferably cerebral vasospasms are detected as a component, including without limitation, those conditions listed under Utility of the Invention.

Symptoms: The common symptom to all these conditions is the vasospasm, particularly cerebral vasospasm.

Testing: Transcranial Doppler is the most preferred test, both for diagnosis and also for titrating dosage of the vasodilators preferred for treatment. Other tests will preferably be used as discussed under Methodology. Generally intracranial blood velocities greater than 0.6 meters/ second, are indicative of vasospasm. Generalized cerebral vasospasm is identified by TCD Mean Flow Velocities (MFV) of greater than 0.1, more preferably than 0.3 and particularly greater than 0.4 meters/second in intracranial vessels (about 0.07, 0.2 and 0.4 meters/second, respectively, for vertebrobasilar system) and prolonged diastolic flow component in which continued elevation of diastolic flow beyond end diastolic velocity occurs throughout substantially the entire course of diastole. This prolonged diastole is the most preferred indicator of vasospasm. Other presently available tests which are valuable for vasospasm detection and dosage titration comprise SPECT nuclear medicine testing, angiograms, EEG, qEEG, P300, and other neuropsycological, psychological and electrophysiological tests which can monitor mental impairment due to vasospasm.

Vasodilator: Nitroglycerine is the most preferred vasodilator for the treatment of the invention, both because of its ready availability in a variety of forms; pill, patch, ointment, cream, spray, inhaler, etc., and because its pharmacology is so well known. The many Nitroglycerine equivalents and substitutes, such as p.o. clonidine, Dynacirc (isradipine), hydrazine, or long acting nifedipine and others known to the art, can be used to replace or to supplement Nitroglycerine. For patients exhibiting Nitroglycerine intolerance, a combination of Nitroglycerine (spray or patch) with Nifedipine is particularly preferred.

Alpha blockers have been tried. Hytrin (Terazosin) has not been found to be effective. Catapress (Clonidine) has been extremely effective. Minipress (Prazosin) has been significantly effective and frequently better tolerated in the long run than Clonidine, although in Applicant's patients, it seems to treat the problem successfully enough to prevent the symptoms, but not enough to allow complete resolution of the vasospasm. Cardura (Doxazosin) has been a relatively mild medication. Aldomet (Methyldopa) has been useful in some patients. Reserpine has been an extremely effective medication. In the short term, it is helpful due to the parasympathomimetic effect, which tends to decrease the activity of the Sumpathetic nervous system. Later, its direct sympatholytic action is very effective. Frequently, a dose needs to be adjusted downward approximately 6-10 weeks after institution of therapy. It has even been useful in treating migraine induced depression due to chronic vasospasm with or without headache in those patients who could not tolerate other vasodilators. Clonidine has also been useful in these depressed patients who could not respond to other vasodilating medications.

ACE inhibitors are effective. With use of ACE inhibitors and concomitant administration of low dose Nitroglycerin, 1/10th inch once a day to several times a day, most patients may be eventually weaned from the use of oral medications, although Applicant does tend to maintain them on low dose Nitroglycerin in perpetuity. Other Angiotensin Converting Enzyme Inhibitors, including Capoten (Captopril), Altace (Ramipril), Lotensin (Benazepril), Monopril (Fosinopril), Prinivil (Lisinopril), Vasotech (Enalapril), and an ACE inhibitor have also been tried. Applicant suspects that ACE inhibitors work the best due to their activity on the Nitric Oxide pathway. They are most effective at reversing the vasospasm when used in conjunction with low dose nitrates.

Calcium channel blockers are effective. The most effective has been Dynacirc (Isradapine). Much less effective have been, in descending order of effectiveness, Nifedipine, Nimodopine, Plendil (Felodipine), Dilacor (Diltiazem), Cardene (Nicardipine) and, Norvasc (Amlodopine) and finally, Verapamil.

Other agents that deserve special mention include Toradol IM in doses of 90-120mg. In lower doses, this is not so effective. Unfortunately, due to the new FDA guidelines, Applicant no longer uses this medication in these doses. Hydralazine is effective, but tends to cause significant blood pressure changes in these patients. Interestingly though, Hydralazine tends to improve the morphology of the diastolic flow component dramatically, which in view of Hydralazine's effect on arterioles, bolsters the perspective that the diastolic phase of the Transcranial Doppler is a good indicator of downstream runoff.

Psychiatric agents frequently have vasoactive effects. Prozac, and other non-vasoconstricting medications are helpful.

As examples of the many drugs available: Clonidine has been extremely effective. Hytrin (Terazosin), Ismelin (Guanethidine), Minipress (Prazosin),have been all tried, with less successful results. Cardura (Doxazosin) is still being tried, but initial results are just now coming available. Dibenzyline (Phenoxybenzamine) beta blockers, Inderal (Propranolol), Tenormin (Atenolol), Normodyne (Labetolol), Lopressor (Metoprolol) Imitrex (Sumatriptan), IM Toradol (Ketoralac) Channel Blocker, and an ACE inhibitor along with low dose Nitroglycerine and a Clonidine patch, as well as magnesium, Brethine, etc.

Accupril (Quinapril), Altace (Ramipril), Capoten(Captopril), Lotensin (Benazepril), Monopril (Fosinopril), Prinivil (Lisinopril), Zestril (Lisinopril timed released), Univasc (Moexipril), Vasotec (Elalapril), Cozaar (Losartan). Accupril (Quinapril) has Inderal (Propranolol), Tenormin (Atenolol), Normodyne (Labetolol), Lopressor (Metoprolol) Angiotensin Converting Enzyme Inhibitors (ACE) inhibitors have been tried including Accupril (Quinapril), Altace (Ramipril), Capoten(Captopril), Lotensin (Benazepril), Monopril (Fosinopril), Prinivil (Lisinopril), Zestril (Lisinopril timed released), Univasc (Moexipril), Vasotec (Elalapril), Cozaar (Losartan). Accupril (Quinapril) has consistently been the most effective. p.o. clonidine, Dynacirc (isradipine), hydrazine, Adalat (Nifedipine) in standard doses and timed release dosages has been helpful but as a second line drug. Careen (Nicardipine), Nimotop (Nimodopine), Cardizem (Diltiazem), Norvasc (AmlodipineMellaril (Thioridizine) has not been effective. Thorazine Chlorpromazine) has been moderately effective. Navane (Thiothixene) has been extremely effective.

All of the effective medications have the common characteristic of causing smooth muscle relaxation and reduce pulmonary capillary wedge pressure in most cases, which empirically defines a class of useful medications which also includes many other medications, some of which are setforth in Appendix A, filed with this application.

Dosage: It is an important feature of the invention that the vasodilator dosage is substantially lower than dosage usually prescribed for treatment

of coronary disease, preferably about 1 to 40%, more preferably 5 to 30, and most preferably 10 to 25% of such conventional dosage. Based on a 70 kilogram patient, on a Nitroglycerine-equivalent basis, about 0.001 to 5000, more preferably about 0.01 to 1000 and most preferably 0.02 to 20 milligrams per day of vasodilator will be optimal in most cases. Still lower rates will be employed on pediatric, and lower body weight adult, patients. Stated differently, from about 10 minutes to 20 hours or even more per day of application of a commercial Nitroglycerine patch can be administered during initial treatment. Further, this dosage will be optimized by reducing or increasing the dosage in response to continuing test results, particularly TCD and qEEG, showing reduction in frequency and/or severity of the patient's vasospasms. In most cases, just sufficient vasodilator will be administered to achieve optimum reduction in vasospasms (preferably measured as optimal TCD Mean Flow Velocity (MFV) at the respective stage of treatment. It will be recognized that these dosages are mainly far lower than the vasodilator dosages commonly employed to treat cardiac disease and this is because the treatment of vasospasm needs much lower dosage, and that vasospasm may even be induced by the vascular reaction to high dosages of vasodilator. Without being bound to any theory, it appears that the number of receptors increases during treatment, so that some patients are able to tolerate only lower dosages as treatment continues. Thus, the "titration" of dosage from time to time on the basis of test results is stressed in the present application.

Duration: Because of the discovery that the vasospasms are not merely acute, but are chronic, treatment duration will be prolonged in most cases, extending over months and even years in some cases. Typically treatments will extend over about 5 to 250 weeks, more preferably 8 to 100, and most preferably 12 to 60 weeks, though treatment duration will be controlled by the patient's response as indicated by the continuing testing..

Titration: Frequent testing, as much as even several TCDs in a single day during initial treatment, will be used to titrate dosage so as to avoid overdose (which can itself trigger vasospasms) as the patient's condition improves.

Delivery Systems: The average dosage on a typical patient will be in the range of roughly one milligram per day. It is desirable to have delivery systems, sprays, ointments, creams, inhalers, and preferably patches of reduced delivery as compared to the conventional systems now available commercially. Such reduced delivery systems are particularly desirable for patients who tend to be too noncompliant, e.g. mentally impaired, to follow reliably a treatment regimen of intermittently applying and removing conventional patches to reduce dosage. Such vasodilator delivery systems will preferably be marked (or packed) with the appropriate DRG and/or ICD

9th. codes and/or instructions for titrating and tapering their use, to facilitate their proper application.

I. Utility of the Invention

This technique is useful in treating a variety of conditions including closed head injury with vasospasm, attention deficit disorder with vasospasm, migraine with inter-ictal evidence of vasospasm, syncope or blackout spells of unknown aetiology with evidence of vasospasm, seizure with evidence of vasospasm, and dementia with evidence of vasospasm, and post-concussion syndrome with evidence of vasospasm, migraine, post-concussion syndrome, sympathetic vasospasm associated with breast implants, and cerebral vasospasm. The invention embodies the discovery that such vasospasms are a component symptom of many whiplash injuries.

While less studied at present, the invention can be used to diagnose and treat the following other diseases which have now been found to frequently involve vasospasms: neurocognative disorders such as, dyslexia, memory disturbances, depression, psychosis, reflex sympathetic dystrophy, mood disorders and sensory motor disorders; transient ischemic attack (TIA), pseudoseizure, hemibalism, and stroke; tremor, Parkinson's disease, torticollis, electrical shock trauma, as well as any other disease in which vasospasm can be detected as a component of symptoms. Even cases of Benign Prostate Hypertrophy (BPH) can be treated with the vasodilators of the invention to relax the smooth *muscle* of the sphincter (where the vasodilator relaxes the muscle even where vasospasm is not a symptom) allowing better emptying of the bladder. Further clinical testing has also established the usefulness in some cases, of additional diseases which have now been found unexpectedly to involve a substantial degree of vasospasm, comprising; vertigo, autism, depression, psychosis, transient global amnesia, memory disabilities, balance disabilities, Tourette's Syndrome, Tinnnitis, Multiple Sclerosis and Multiple Sclerosis-like syndrome, hyperactivity and Attention Deficit Disorder, deficits resulting from strokes of various causes, migraine, seizures, balance disorders, concussion, post-concussion syndrome sometimes including temporal mandible joint pain (TMJ) or facial pain, cerebral ischemia and other vascular components discovered to be associated symptoms in some cases of psychiatric disorders such as chronic depression and some psychosis, as well as vascular dysfunction from any cause such as kidney disease and peripheral vascular disease e.g. from diabetes, cholesterol, infection or other cause. A basic factor is that neurological diseases are really symptom diagnoses for the most part. Thus depression is the diagnosis for a specific type of behavioral abnormality, not the underlying pathological or anatomical diagnosis. This is also true for stroke, multiple sclerosis, vertigo, balance disorders, and many other diseases may be directly caused by ischemia, or have a component of their

problem caused by ischemia, or have associated problems caused by vasospasm arising from their associated problems.

Brief Description of the Drawings

Figure 1 is a Transcranial Doppler (TCD) of MCA immediately prior to treatment by Nitroglycerine spray.

Figure 2 is a TCD of MCA post Nitroglycerine spray obtained during continuous monitoring.

Figure 3 is a related raw EEG scan.

Figure 4 is a brainmap showing a spatial distribution of alpha frequency mu rhythm.

Figure 5 is a brainmap showing a spatial distribution of beta frequency mu rhythm.

Description of the Preferred Embodiments

Examples - Whiplash, MS, Migraine

A clinical review and correlation among 38 whiplash patients, 19 patients with MS-like syndrome, one with MS associated with breast implants, as well as 5 migraine patients is presented. All patients have similar clinical complaints, EEG abnormalities, and cerebral vasospasm identified on Transcranial Doppler testing. All have similar clinical responses to medication that resulted in clinical improvement paralleling the course of clinical resolution of the cerebral vasospasm.

METHODOLOGY: All patients are evaluated with a complete history, physical exam, and neurological exam by a Board Certified Neurologist. All patients have blood work consisting of a CBC with differential count and platelets as well as an SMA-30 obtained. All whiplash related patients underwent a CT or MRI of the brain, EEG and qEEG, B-mode and spectral analysis ultrasound of the subclavian, carotid, and vertebral circulation, and Transcranial Doppler (TCD) examination of the intracranial circulation. In some situations, repetitive Transcranial Doppler examinations are performed on the same patient in the same day. Initially, these tests are performed by maintaining the probe on the patient's head through the course of several hours, but later the technique involves using the same probe, patient position, technician, depth, and cranial window with serial but interrupted exams across the course of the day. In all cases, the highest spectral frequencies are recorded, as well as repeat exams at the same depth and window as the baseline pre-medication windows were obtained. Immediately prior to initial TCD exams, a neurological exam is carried out. At the time of initiation of treatment for the cerebral vasospasm, at which time vasoactive medications are administered after the baseline TCD and

neuro exam are obtained, repeat TCD exams are carried out and when medication effects on the intracranial circulation were identified, repeat neurological exams are obtained. In 5 patients, P300 are obtained prior to initiation of treatment and, again, several months later. The same methodology is used in those patients referred for evaluation of possible MS-like syndrome as recognized in the recent global settlement. With these patients, triple evoked potentials, EEG and qEEG, and a vascular evaluation as outlined above is carried out in all patients, and in 11 who decided to attempt treatment with vasoactive drugs, the methodology outlined above for initiation of as in the MVA-related post-concussion syndrome are used. 10 of the 19 MS-like syndrome patients additionally had brain MRI tests performed. In 3 of the MS-like syndrome patients, P300 tests are obtained and serial studies after 1-2 months of treatment in all 3 were also obtained. The same methodology are also used with respect to the patients with a history of migraine, although only two of these had MRI or head CT exams performed at time of initiation of treatment. All 5 had carried a diagnosis of migraine headache for at least 10 years prior to evaluation.

All patients noted that these symptoms are intermittent in occurrence, and at times some symptoms would coexist with other symptoms, and at other times these symptoms would be dissociated each from the other. All noted that the symptoms could be aggravated by stress. All patients had tried over the counter and prescription anti-inflammatories and muscle relaxants prior to and during the initial stages of evaluation without significant relief. All had been tried on Fioricet or Fiorinal, Midrin (isometheptene mucate), and aspirin. 22 of the 38 patients had also been tried on calcium channel blockers, beta blockers, Imitrex (sumatriptan succinate), and p.o. Toradol (ketorolac tromethamine). 21 of the 38 used narcotics for pain control. Neurological exam on these patients are remarkable, during exacerbation, for lower extremity hyperreflexia, abnormal tandem gait, and abnormal Rhomberg exam. All patients' examinations could be aggravated by inducing psychological stress in the patients or performing actions that increased their pain, as would occur by doing activities that would aggravate their neck discomfort. All patients had normal MRI or CT examination of the brain. EEG and qEEG exams are performed on each of these patients, with the following findings. All patients had a low voltage 5-20 microvolt polymorphic delta and theta pattern identified in the frontal and temporal areas. Those who complained of ataxia and balance disturbance had the same abnormalities identified in the occipital lobe. All had a superimposed mu rhythm in the frontal and temporal areas better identified on qEEG than on bipolar montages as this rhythm appeared as a subharmonic superimposed over the posterior occipital alpha rhythm on the bipolar montage. The qEEG, a 16 channel average referential montage, allowed

improved definition of wave form analysis and spatial distributions and confirmed the underlying EEG evaluations. TCD exams in all patients showed evidence of generalized cerebral vasospasm as identified by Mean Flow Velocities (MFV) of greater than 0.1, more preferably 0.2 and most preferably 0.4 meters/second in intracranial vessels (about 0.06, preferably 0.2 and most preferably 0.3 meters/second for vertebrobasilar system) and prolonged diastolic flow component in which continued elevation of diastolic flow beyond end diastolic velocity occurs throughout the entire course of diastole. In all cases, the EEG and qEEG abnormalities mirrored the distribution of vascular abnormalities identified on Transcranial Doppler.

RESULTS: 38 patients referred with post-concussion syndrome after whiplash due to fall, motor vehicle accident (MVA), or beating are evaluated. On initial evaluation, their clinical complaints included intermittent headache, photophobia, visual blurring or transient scotomas, hyperacusis, word finding or word substitution problems, ataxia or balance disturbance, memory and concentration lapses, and, in some cases, black out spells associated with syncope. A baseline blood pressure, neurological exam and TCD are then obtained at the time of initiation of treatment, and treatment are initiated with nitroglycerin sublingual spray. Initially, continuous TCD monitoring was performed for out to two hours from administering the spray. Continuous monitoring was performed of that vessel previously identified to be in the most severe spasm. Ongoing monitoring of blood pressure and pulse with an electronic monitor was also performed. When pharmacological relaxation had peaked, repeat neurological exams are performed as well as patient's clinical perspectives on their symptoms are sought.

All patients showed improvement in Mean Flow Velocities at 15 minutes who are continuously monitored, and the peak degree of relaxation was seen at 1 hour with continued relaxation of the intracranial spasm identified out to two hours. At the time of peak relaxation, approximately 1-2 hours out from administration of the nitroglycerin or other vasoactive drugs, a full TCD and neurological exam was carried out. No blood pressure changes, including orthostatic changes, of significance are noted as defined as changes in systolic or diastolic readings of 10 points or greater and changes in pulse of 10 points or greater. Generally no changes in pulse or blood pressure are noted beyond changes of less than 5 points in any of the readings. Continuous TCD monitoring was performed in 9 patients. Serial TCD monitoring was performed in 25 patients, usually at 45-60 minutes post administration. All patients showed clinical improvement, however 3 patients did not show significant TCD improvement. These

patients are subsequently identified as unable to tolerate Nitroglycerine and are nitrite sensitive. In those patients who are continuing to be monitored, they redeveloped their subjective symptoms and objective exam abnormalities as the vasospasm returned as documented on TCD.

The TCD exam became vital for individualizing treatment. It was found that the therapeutic window for Nitroglycerine changed over the first 3 months of treatment and patients frequently redeveloped their symptoms or developed migraine headaches. Here the TCD was vital for modifying treatment. In these patients, while on Nitroglycerine, a repeat TCD is obtained and then a therapeutic challenge is administered by spray. Repeat TCD is obtained at 15 minute and 1 hour intervals. Those patients who had developed a Nitroglycerine-induced migraine or migraine equivalent mirroring or superimposed on their original problem developed worsening of the TCD at the 15 minute or the 1 hour interval. Those who required increases in their dose, showed improvement of Mean Flow Velocity on TCD. 1 patient who had previously failed Nitroglycerine spray or patch alone due to a nitrite sensitivity, and failed Nifedipine alone, is able to tolerate the two in a combined dose with virtual complete resolution of clinical symptoms as confirmed by history, exam, and TCD findings. With removal of the Nitroglycerine, while any degree of abnormalities are still seen on TCD, applicant's patients' problems recur. However, with continuing treatment until Mean Flow Velocity has returned to normal and is documented as normal during Nitroglycerine free intervals during the day, the patients could then use the Nitroglycerine spray or patch on a PRN basis for treatment of any of the above mentioned complaints with great success rather than continuing to require scheduled daily doses of medication.

While most patients eventually reached a peak daily dosage of 4-6 hours in two to three divided doses on a nitroglycerin patch during treatment, dosage requirements varied from 10 minutes a day in two adolescent girls, and one 30 year old male, up to a total of 24 hours a day for one 34 year old woman whose initial complaints prior to starting the Nitrodur (nitroglycerin) patch included severe ataxia, confusion and intermittent syncope or episodes of hemiparesis in addition to the visual blurring, headaches and concentration and memory changes seen in the other patients.

Most patients are on this dose for 1-2 months, and then tapered. No patients who are able to tolerate Nitroglycerine treatment continued to require narcotics, and only two of the above patients in this series remained on narcotics where 21 of the 38 who started treatment are on narcotics for pain control. Of great significance is that 2 patients with intermittent syncope also have episodic hemiplegic migraines. They showed complete resolution of both of these problems shortly into therapy. There are only 3 failures to treatment. 1 patient with post-traumatic syncope of unknown

aetiology who is nitrite sensitive continued with these episodes, and one such episode is brought on by 3 minutes of a Nitrodur patch being applied. She eventually responds to maintenance treatment with p.o. hydralazine in doses high enough to treat the vasospasm. The second patient is unable to tolerate Nitroglycerine or short-acting nifedipine, which caused angina, but did respond to Adalat, a long acting nifedipine preparation. The third continued on narcotics at low doses but unchanged from the dose she presented on.

Applicant's patients range in age from 15-76, consisting of 12 men and 26 women. In four patients with post-traumatic fibromyalgia and fibromyositis, the symptoms of fibromyalgia and fibromyositis completely resolve while on Nitroglycerine. They are in the tapering phase, and the symptoms are not recurring of these fibromyositic and fibromyalgic conditions. The P300 in the 5 patients evaluated also shows improvement during the course of treatment. In 3 of these patients, this improvement is independently confirmed by the neuropsychologists treating the patient. The other patients do not have ongoing neuropsychological follow-up. Figures 1 and 2 represent examples of the baseline TCD while patient is symptomatic, and a follow-up TCD with resolution of patient's complaints after a Nitroglycerine sublingual spray. Figures 3, 4 & 5 represent examples of raw EEG tracing obtained on an average referential montage and two accompanying qEEG epochs. The first brainmap, Figure 4, shows examples of the distribution of the alpha frequency mu rhythm, frontally, temporally, and occipitally; and the second, Figure 5, is similar but shows that these mu rhythm frequencies are frequently in the beta range. On these maps, the frontal lobe is to the top, and the occipital lobe is inferior.

In 19 patients with MS-like syndrome and 1 with MS associated with breast implants, a similar pattern of complaints, Electro- encephalographic and TCD findings is seen. Our patients range in age from 23 - 61. The pattern of complaints is the same as the whiplash patients. Headache, concentration and memory disturbances, visual blurring, intermittent focusing abnormalities, balance disturbances, ataxia, photophobia, and hyperacusis are complained of in all patients. The severity of the complaints, however, tends to be less than that of the whiplash patients, however, their complaints of memory and cognitive dysfunction and mood swings tend to be considered by the patient to be their most severe problem in all but the one case who is felt to have MS. Of the 10 patients who had MRI's performed, 2 had a few scattered UBO's consistent with small white matter infarcts, and one had large plaques consistent with MS on MRI and brain biopsy. All patients had fibromyalgia and fibromyositis.

All but one of the patients had MRI or surgical confirmation of implant rupture and in that one patient, it is clinically suspected due to patient's symptoms, their progression, and length of time of implant (20

years). All patients had the same constellation of EEG and qEEG abnormalities, TCD abnormalities that paralleled the vascular distribution of the EEG changes in a fashion identical to that seen in the whiplash patients and that followed clinical distributions subserved by vasculature.

11 patients decided to start treatment with vasoactive medications. 10 started initially with IM Toradol, followed by maintenance dosing of Toradol given by mouth is seen to give consistent improvement clinically and with respect to the TCD. Unfortunately, gastritis developed in all cases and the patients are switched to Nitroglycerine by spray and patch, and is joined by the 11th patient, who initiated treatment with Nitroglycerine. Again, using the method outlined for initiating treatment with the MVA patients, baseline blood pressures, neuro exams, and TCD exams are performed with serial examinations on the first day also carried out as previously discussed. Results are identical. All patients have dramatic clinical improvement in exam and clinical symptoms with resolution of vasospasm as documented on TCD. All patients relapse as the initial dose of medication wears off as again documented by TCD. Although no patients are found to be nitrite sensitive in this group of patients, the TCD again became invaluable in monitoring and modifying dosage regimens. Interestingly, unlike the whiplash related patients, most of whom are able to taper their use of the nitroglycerin use within three- four months of treatment initiation without requiring the use of other medications, none of the breast implant cases have been able to dramatically reduce their need for the medication below a Nitrodur 0.1 mg patch for 4 hours a day. Again, the therapeutic window for Nitroglycerine modified in these patients over time, the TCD became again invaluable for individualizing the dose necessary for treatment. In all patients who started the Nitroglycerine treatment, the symptoms of fibromyalgia and fibromyositis resolved while on therapy and returned if they stopped therapy.

Five patients had a history of intermittent migraine headache, with only one patient noticing intermittently a history of scintillating scotoma as a prodrome to the headache. Later, after treatment had been initiated, all reported that they could start to recognize prodromes that they previously did not consider as prodromes. These included mild balance disturbance, feeling of a mildly clouded sensorium, or abrupt sensation of severe fatigue of acute onset. All 5 patients are men, ages 37-58. All showed evidence of vasospasm on TCD and the headache resolved with Nitroglycerine patches applied for 10 minutes to 1 hour. Follow-up TCD at the end of application of the patch are obtained in 3 patients which confirmed reduction of the vasospasm. At the time of symptomatic treatment, all patients had minimal lower extremity hyper-reflexia, and a minimally abnormal test on Rhomberg exam and tandem gait testing. These abnormalities all resolved with the nitroglycerin.

DISCUSSION: In applicant's practice, the association of cerebral vasospasm is consistently found to be associated with a typical clinical complex. This complex includes complaints of balance and memory problems, intermittent visual blurring, scotomas, or difficulty focusing, intermittent photophobia, and/or hyperacusis, memory and concentration lapses, word finding difficulties, dysaphasias; and, in more severe cases, headache which sometimes progresses to hemiplegic migraine with documentable weakness, asymmetric reflexic changes or fanning of toes or further progression to headache associated syncope or syncope with tonic/clonic activity and post-ictal confusion. Neurological exam most consistently shows a positive Rhomberg exam, abnormal tandem gait, and in more severe cases showed fanning of toes or intermittent Babinski's and reflex changes. The symptoms and neurological exam wax and wane in severity of abnormalities. In whiplash patients, the exam worsens with psychological stress or pain, and, in the breast implant patients, psychological stress would precipitate a worsening of the exam. The patients often appeared to be photophobic or would startle easily to sound. EEG and qEEG's, even those with syncope or syncope and secondary, observed, tonic/clonic activity, would be minimally abnormal. However, the pattern of EEG abnormalities, as well as the subjective complaints and neurological exam findings, mirrored the vascular distribution of the abnormalities seen on TCD. Interestingly, this syndrome in the whiplash patient and the breast implant patient has now been found to only rarely develop immediately with the causative trauma, but instead to develop over a time course of weeks to many months after the initiating irritant.

In the early stages of treatment of these patients, applicant monitors specific vessels continuously while giving patients test doses of medication. applicant did this in order to more quickly evaluate which medications are most effective for each patient and to individualize doses. It became clear that such extensive and time-consuming studies are not necessary, as this condition of cerebral vasospasm in these patients is a generalized phenomenon to the cerebral circulation. The problem is probably systematically generalized as common associated complaints during times of these previously mentioned complaints include prinz-metal type angina, intermittent coolness of the extremities to the touch, and menstrual cycle irregularities in some women. All of these symptoms, except for the menstrual cycle irregularities would be aggravated by stress and are improved by treatment with the vasoactive drugs. BAER studies are initially performed on many patients as part of the evaluation of the ataxia, but are not helpful as they frequently are abnormal if vertebral artery spasm is seen on TCD. The BAER abnormalities resolved with resolution of the TCD spasms in those where applicant has had the opportunity to repeat the

study. Significantly, though, those with abnormal BAER's at institution of therapy, had more severe reactions to the initial stages of treatment with Nitroglycerine and reported more severe reactions when they had previously been treated with vaso-constrictive medications for headache control. It has now been found that Nitroglycerine, in the early stages of administration, can give transient severe *vasoconstrictive* episodes, apparently due to a hypersensitivity reaction in which, during early administration of the drug, some individuals develop transient worsening of the vasospasm which may result clinically in migraine headache, seizure, or syncope. In some cases, such episodes can be mistaken for stroke.
Thus, great care must be used in administering this drug to someone in the midst of an exacerbation. In applicant's practice, the first dose of Nitroglycerine is always given under direct physician observation, immediately after obtaining a baseline TCD. This is done as those patients with the most severe reactions to Nitroglycerine generally, but not invariably, had the most severe abnormalities on TCD, or are patients severely symptomatic for a long time, or are less than the age of 20. This transient supersensitivity may be witnessed on TCD but did not occur with any of the other vasodilating medications applicant has tried, specifically, p.o. clonidine, Dynacirc (isradipine), hydralazine, or long acting nifedipine. It, clinically, probably does occur in some patients after administration of the short acting form of nifedipine but applicant has not personally witnessed the TCD reactions for this drug as applicant has with the other mentioned drugs.

Multiple other vasoactive medications are tried on these patients prior to attempting nitroglycerin. Those medications that caused vasoconstriction on the TCD, such as Stadol (butorphanol tartrate), DHE, and Imitrex, in every case worsened the patient's neurological exam and mentation but improved their headache. However, in applicant's patients, the more serious neurological events such as syncope, TIA, or seizures, are usually preceded by a headache. Due to applicant's concern that headaches may be a significant warning sign of impending serious neurological events, the cerebral equivalent of angina, applicant attempted vasodilator to reduce the vasospasm. Those that resulted in vascular dilatation, such as Toradol, Nitroglycerine, clonidine, hydralazine, Dynacirc, and long acting forms of nifedipine, all resulted in clinical and neurological exam improvement mirroring the TCD exam's improvement. These medications also alleviated or treated the headache. All medications in this and generally reduce pulmonary capillary wedge pressure, which empirically defines a class of useful medications.

Common clinical symptoms of headache, intermittent visual abnormalities, ataxia or balance troubles in patients with usually normal

brain CT or MRI scans but abnormal EEG and TCD findings suggestive of cerebral vasospasm are presented. These patients are found to have a clinical aggravation of their symptoms directly related to the degree of vasospasm seen on TCD. Techniques which modified this vasospasm could cause clinical improvement or worsening paralleling the degree of severity seen on TCD. This application is not meant as a final recipe for the treatment of cerebral vasospasm on the outpatient basis, but instead is meant to provide basis for further study into the mechanism of these findings in disparate conditions and possibilities for treatment.

Applicant believes he is the first to identify vasospasm in patients with the condition whiplash. Half of these patients are also identified as having either closed head injury symptoms or post-concussion syndrome symptoms. These patients have neuropsychological testings which for the most part confirmed the findings of closed head injury in the previously mentioned half of the group.

In treatment of patients with migraine headache, the present state of the art is to treat patients with migraine with vasoconstricting medications as opposed to vasodilation medications, and in fact the present state of treatment of these conditions with the vasodilating medications mentioned is considered that the vasodilator may cause migraine headaches. Additionally, applicant has four patients with attention deficit disorder and four patients with seizure, all with vasospasm and all of which have responded well seen from both neuropsychological testing or seizure control with the use of vasodilator as described herein. In summary, vasospasm has been discovered to be a clinically common and treatable entity.

In FDA attachments for medications in which migraine headache is identified as a side effect, no indications for the previously mentioned treatments are identified.

Additionally, good results are obtained in a number or patients presenting with systemic disorders, including cases of fibromyalgia, cardiac disease and even gastric disorders, by testing and treatment to reduce or eliminate vasospasms according to the techniques described above. Still further study after the filing of the provisional application shows good results in the treatment of additional diseases which have now been found unexpectedly to involve a substantial degree of vasospasm, comprising hyperactivity and Attention Deficit Disorder, deficits resulting from strokes of various causes, migraine, seizures, balance disorders, concussion, post-concussion syndrome sometimes including temporal mandible joint pain (TMJ) or facial pain, cerebral ischemia and other vascular components discovered to be associated symptoms in some cases of psychiatric disorders such as chronic depression and some psychosis. For brevity Appendix A (based on papers to

be published) gives clinical details and the following Examples summarize the clinical treatment and results.

While the diseases to which the new techniques have been found applicable seem to be disparate and unconnected, the modality bridging all of them appears to be the relaxation of smooth muscle tissue by treatment with low dosage of vasodilator and the titration of this dosage over time to avoid overdosage as the patient's response to the medication changes. Thus, relaxation of smooth muscles underlying the vascular system alleviates vasospasm, the relaxation of spincter muscles alleveates BPH, and the relaxation of downstream arteries alleviates the effect even of physical buildup of cholesterol.

Example - Attention Deficit Disorder

Attention Deficit Disorder has been found to affect more than 12 percent of the school age population. This disorder has now been found to continue into adulthood and many ADD adults with a mild condition had proceeded through life undetected. Limited blood flow to the brain (cranial perfusion) has been postulated as a cause for this condition. Two adults, siblings, were evaluated and treated as taught herein,(a regimen was made up of a low dose Calcium Channel Blocker, and an ACE inhibitor along with low dose Nitroglycerine and a Clonidine patch), to increase blood flow to the brain with results showing increased social and emotional control of themselves and IQ improvement of approximately 30 points. Also they improved in achievement motivation and specific goals for their lives.

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

It was discovered that most patients referred to a neurologist's office for brain injury or concussion do not have a brain injury. Rather, they have an injury to the control mechanism that controls blood flow to the brain. This injury results in causing blood flow to the brain to decrease. This drop off in blood flow accounts for all or much of the clinical symptoms. It is reversible. Of 22 patients randomly identified by computer with presenting symptoms of brain injury and a diagnosis of concussion, one third had no brain injury, but only a vascular disorder, and the other two thirds identified that a significant portion, or all of their symptoms were alleviated with the use of common vasodilating medication. A further aspect was that 22 out of 22 patients referred for evaluation of closed head injury and concussion complained, on careful questioning, of their symptoms becoming worse as time went on. These symptoms that developed or worsened progressively were reversed with vasodilating medication.

EXAMPLE - PSYCHOSIS CAUSED BY CEREBRAL ISCHEMIA

In this Example, a patient who has an acute psychotic break is presented. The patient is identified as having a history of migraines and then developing acute schizophrenia. She is hospitalized for an acute psychotic break. Due to difficulty in controlling the thought disorder, the hospitalization is extended for 3 weeks. She is then released and self-discontinued her medications. Out-patient evaluation of her reveals that the blood vessels leading into her brain are overly constricted, and she is placed on medication to dilate these blood vessels. The patient's thought disorder processes, memory disturbances and headaches completely resolve. This represents a new approach to the diagnosis and treatment of psychosis and underlying concerns.

EXAMPLE - REVERSING STROKE USING COMMON VASODILATORS

In this Example, three patients with strokes improved dramatically in minutes to days after devastating strokes by using the new therapy taught herein (e.g. Dynacirc 10 mg t.i.d. and repetitive uses of Nitroglycerin.) The first patient developed a large stroke, which caused her to be able to walk only with assistance and a cane, and not to be able to speak her thoughts. One month later, no major clinical changes had occurred. Within 45 minutes of instituting the present therapy, she can walk unassisted, speak normally and had only minimal weakness. By the next day, she can transfer from a dock to a boat unassisted. The second patient has been paralyzed for one year on his left side. Within one month, he has regained 80% of his strength throughout most of his body. Within four months he can lift 300 pounds with his paralyzed leg and 120 pounds with his previously paralyzed arm. The third patient has severe weakness in his right arm and face for four days. Within one hour of starting treatment, he has regained most of the use of his arm. Nitroglycerin and other medications all result in improvement in the patient's headache, but also resulted in improvement of any other neurological abnormalities including balance disorders, gait disorders, hemiparesis, abnormal Babinski's and abnormal reflexes.

Modifications

Specific compositions, methods, or embodiments discussed are intended to be only illustrative of the invention disclosed by this specification. Variation on these compositions, methods, or embodiments are readily apparent to a person of skill in the art based upon the teachings of this specification and are therefore intended to be included as part of the inventions disclosed herein.

For example, the vasodilators include many that are not named here, the tests for vasospasm are constantly improving and it will be evident that new tests for blood flow and others not named here will be useful in the step of

testing for vasospasm described in this application and that the treatable diseases will expand as vasospasm is found to be a component of additional diseases. Reference to documents made in the specification is intended to result in such patents or literature being expressly incorporated herein by reference.